

AMENDMENT

Please enter the following amendments. Deleted subject matter is indicated with strikethrough text and added subject matter is indicated with underlined text. The current listing of Claims supersedes all previous versions.

In the Claims

1. (Withdrawn) An implantable medical device comprising (a) at least one biocompatible matrix polymer region and (b) bioactive agents comprising an antimicrobial agent and a microbial attachment/biofilm synthesis inhibitor.
2. (Withdrawn) The medical device of claim 1, wherein both the antimicrobial agent and microbial attachment/biofilm synthesis inhibitor are present in a single distinct matrix polymer region.
3. (Withdrawn) The medical device of claim 1, wherein the antimicrobial agent and the microbial attachment/biofilm synthesis inhibitor are present in distinct matrix polymer regions.
4. (Withdrawn) The medical device of claim 1, wherein said antimicrobial agent is present in an amount effective to inhibit the growth of microbes on and around the device and the microbial attachment/biofilm synthesis inhibitor is present in an amount effective to inhibit the attachment of microbes onto and the synthesis and accumulation of biofilm from attached microbes on the surface of the device.
5. (Withdrawn) The medical device of claim 1, wherein said device is adapted to remain implanted for a period of greater than about 30 days.
6. (Withdrawn) The medical device of claim 1, wherein said matrix polymer comprises a biocompatible biodegradable polymer.
7. (Withdrawn) The medical device of claim 1, wherein said matrix polymer comprises a

biocompatible non-biodegradable polymer.

8. (Withdrawn) The medical device of claim 7, wherein said non-biodegradable polymer is selected from the group consisting of ethylene vinyl acetate copolymers, copolymers of ethylene with acrylic acid or methacrylic acid, elastomeric polyurethanes and polyurethane copolymers, metallocene catalyzed polyethylene, ionomers and vinyl aromatic copolymers.

9. (Withdrawn) The medical device of claim 6, wherein said biodegradable polymer is selected from the group consisting of polylactic acid, polyglycolic acid, copolymers and mixtures thereof.

10. (Withdrawn) The medical device of claim 8, wherein said non-biodegradable polymer is an ethylene vinyl acetate copolymer.

11. (Withdrawn) The medical device of claim 10, wherein said ethylene vinyl acetate copolymer has a vinyl acetate content of from about 19% to about 28%.

12. (Withdrawn) The medical device of claim 10, wherein said ethylene vinyl acetate copolymer has a vinyl acetate content of from about 3% to about 15%.

13. (Withdrawn) The medical device of claim 1, wherein said antimicrobial agent is selected from the group consisting of triclosan and chlorhexidine and mixtures thereof.

14. (Withdrawn) The medical device of claim 13, wherein said antimicrobial agent is triclosan.

15. (Withdrawn) The medical device of claim 14, wherein said microbial attachment/biofilm synthesis inhibitor is selected from the group consisting of NSAIDs, EDTA and EGTA.

16. (Withdrawn) The medical device of claim 15, wherein said microbial attachment/biofilm synthesis inhibitor is salicylic acid or a salt or derivative thereof.

17. (Withdrawn) The medical device of claim 16, wherein said microbial attachment/biofilm synthesis inhibitor is salicylic acid.

18. (Withdrawn) The medical device of claim 4, wherein the amount of said antimicrobial agent present in said matrix polymer is from about 0.5% to about 25% by weight of the matrix polymer.

19. (Withdrawn) The medical device of claim 4, wherein the amount of said microbial attachment/biofilm synthesis inhibitor present in said matrix polymer is from about 0.5% to about 25% by weight of the matrix polymer.

20. (Withdrawn) The medical device of claim 1, wherein said matrix polymer further comprises a radio-opacifying agent.

21. (Withdrawn) The medical device of claim 20, wherein said radio-opacifying agent comprises bismuth subcarbonate.

22. (Withdrawn) The medical device of claim 20 wherein the amount of said radio-opacifying agent present in said matrix polymer is from about 0.5% to about 45% by weight of the matrix polymer.

23. (Withdrawn) The medical device of claim 1, wherein the matrix polymer further comprises at least one therapeutic agent.

24. (Withdrawn) The medical device of claim 23, wherein the therapeutic agent is selected from the group consisting of chemotherapeutic agents, NSAIDs, steroidal anti-inflammatory agents, and mixtures thereof.

25. (Withdrawn) The medical device of claim 23, wherein the therapeutic agent is selected from the group consisting of cisplatin, methotrexate, doxorubicin, paclitaxel, docetaxel,

dexamethasone, hydrocortisone and prednisone.

26. (Withdrawn) The medical device of claim 1, further comprising one or more barrier layers at least partially covering said at least one matrix polymer region.

27. (Withdrawn) The medical device of claim 26, comprising a first matrix polymer region; a first polymeric barrier layer at least partially covering an interior surface of said first matrix polymer region; and a second polymeric barrier layer at least partially covering an exterior surface of said first matrix polymer region.

28. (Withdrawn) The medical device of claim 27, wherein each of said first matrix polymer region, and said first and second polymeric barrier layers is in the form of an annulus.

29. (Withdrawn) The medical device of claim 28, wherein the first and second polymeric barrier layers comprise the same polymeric materials.

30. (Withdrawn) The medical device of claim 28, wherein the first and second polymeric barrier layers comprise different polymeric materials.

31. (Withdrawn) The medical device of claim 27, further comprising a second and, optionally, a third matrix polymer region and a third and, optionally, a fourth polymeric barrier layer; wherein the second matrix polymer region is disposed on an outside surface of the second polymeric barrier layer and the third polymeric barrier layer at least partially covers an exterior surface of said second matrix polymer region; and, wherein the third matrix polymer region, when present, is disposed on an interior surface of said first polymeric barrier layer and the fourth polymeric barrier layer at least partially covers an interior surface of said third matrix polymer region.

32. (Withdrawn) The medical device of claim 27, wherein the first matrix polymer region comprises an ethylene vinyl acetate copolymer.

33. (Withdrawn) The medical device of claim 32, wherein each of the first and second polymeric barrier layers comprises a material selected from the group consisting of metallocene catalyzed polyethylenes and polyethylene copolymers, ionomers, elastomeric polyurethanes and polyurethane copolymers, ethylene vinyl acetate copolymers and copolymers of ethylene with acrylic acid or methacrylic acid.

34. (Withdrawn) The medical device of claim 33, wherein the antimicrobial agent is selected from the group consisting of triclosan, chlorhexidine and combinations thereof, and the microbial attachment/biofilm synthesis inhibitor is salicylic acid or a salt thereof.

35. (Withdrawn) The medical device of claim 1, wherein the medical device is selected from the group consisting of a stent cover, a biliary stent, a ureteral stent, a pancreatic stent, a urinary catheter, a venous access device, a peritoneal access device, a device connecting or providing drainage between two sterile body environments, and a device connecting or providing drainage between a non-sterile and a sterile body environment.

36. (Withdrawn) The medical device of claim 35, wherein the device comprises a device connecting or providing drainage between a non-sterile and a sterile body environment.

37. (Withdrawn) The medical device of claim 36, wherein the device comprises a hollow tubular structure.

38. (Withdrawn) The medical device of claim 35, wherein the device comprises a stent cover.

39. (Withdrawn) The medical device of claim 38, wherein said biocompatible polymeric matrix comprises polyurethane, said antimicrobial agent comprises triclosan, said microbial attachment/biofilm synthesis inhibitor comprises salicylic acid or a salicylic acid derivative and further comprising a bismuth subcarbonate radio-opacifying agent.

40. (Withdrawn) The medical device of claim 38, wherein the stent cover comprises a hollow tubular structure adapted to be placed over a stent that comprises a woven, knitted or braided open mesh design comprising a biocompatible material.

41. (Withdrawn) The medical device of claim 40, wherein the stent cover is placed over a biliary stent.

42. (Withdrawn) The medical device of claim 40, wherein the biocompatible material is selected from the group consisting of stainless steel or a shape memory material.

43. (Withdrawn) The medical device of claim 35, wherein the medical device comprises a pancreatic stent that provides drainage from the pancreas to the duodenum.

44. (Withdrawn) The medical device of claim 43, wherein the pancreatic stent comprises a buffering agent.

45. (Withdrawn) The medical device of claim 44, wherein said buffering agent, upon exposure to physiological fluids, creates a pancreas-compatible pH level in an environment in which the pancreatic stent is implanted.

46. (Withdrawn) The medical device of claim 45, wherein said buffering agent is a bicarbonate salt.

47. (Withdrawn) The medical device of claim 46, wherein said bicarbonate salt is selected from the group consisting of sodium and potassium bicarbonate.

48. (Withdrawn) A method of manufacturing an implantable or insertable medical device comprising: providing a combination of (a) one or more biocompatible matrix polymers and (b) bioactive agents comprising an antimicrobial agent and a microbial attachment/biofilm synthesis inhibitor; processing said combination under conditions that substantially prevent preferential

partitioning of any of said bioactive agents to a surface of any of said biocompatible matrix polymers and that substantially prevent chemical modification of said bioactive agents.

49. (Withdrawn) The method of claim 48, further comprising controlling either or both of the temperature and moisture content during said processing.

50. (Withdrawn) The method of claim 48, wherein said processing comprises mixing said one or more biocompatible matrix polymers with one or more of said bioactive agents to form a homogeneous mixture of said one or more matrix polymers and said one or more bioactive agents.

51. (Withdrawn) The method of claim 50, wherein said homogeneous mixture comprises both bioactive agents.

52. (Withdrawn) The method of claim 50, wherein said mixing comprises applying mechanical shear to said one or more biocompatible matrix polymers and said one or more bioactive agents with a device selected from the group consisting of a single screw extruder, a twin screw extruder, a banbury mixer, a high-speed mixer and a ross kettle.

53. (Withdrawn) The method of claim 50, where said mixing comprises forming a solvent solution or a liquid dispersion of said one or more bioactive agents and said one or more biocompatible matrix polymers.

54. (Withdrawn) The method of claim 50, further comprising shaping said homogenous mixture into a matrix polymer region of an implantable or insertable medical device.

55. (Withdrawn) The method of claim 54, wherein said shaping comprises a process selected from molding, calendaring, casting and solvent coating.

56. (Withdrawn) The method of claim 54, wherein said shaping comprises extrusion.

57. (Withdrawn) The method of claim 56, wherein said extrusion comprises forming at least one annular matrix polymer region.

58. (Withdrawn) The method of claim 57, further comprising forming at least one polymeric barrier layer at least partially covering a surface of said annular matrix polymer region.

59. (Withdrawn) The method of claim 58, wherein said method comprises a process selected from extrusion coating said polymeric barrier layer onto said annular matrix polymer region and solvent coating said polymeric barrier layer onto said annular matrix polymer region.

60. (Withdrawn) The method of claim 58, wherein said covering comprises coextruding said polymeric barrier layer and said annular matrix polymer region.

61. (Withdrawn) The method of claim 58, forming a first polymeric barrier layer at least partially covering an interior surface of said annular matrix polymer region and forming a second polymeric barrier layer at least partially covering an exterior surface of said annular matrix polymer region.

62. (Withdrawn) The method of claim 61, wherein said covering comprises coextruding said first and second polymer barrier layers with said annular matrix polymer region.

63. (Withdrawn) The method of claim 50, wherein said processing comprises forming homogeneous first and second mixtures of first and second biocompatible matrix polymers and one or more of said bioactive agents and, optionally, forming a homogenous third mixture of a third biocompatible matrix polymer and one or more of said bioactive agents.

64. (Withdrawn) The method of claim 63, comprising coextruding said homogenous first and second mixtures to form first and second annular matrix polymer regions and, optionally, coextruding therewith said homogeneous third mixture to form a third annular matrix polymer region.

65. (Withdrawn) The method of claim 64, further comprising forming at least first and second polymeric barrier layers at least partially covering interior and exterior surfaces of said first annular matrix polymer region; forming a third polymer barrier layer at least partially covering an exterior surface of said second annular matrix polymer region and, optionally, forming a fourth polymeric barrier layer at least partially covering an interior surface of third annular matrix polymer region.

66. (Withdrawn) The method of claim 65, wherein said covering comprises coextruding said first, second and third polymeric barrier layers with said first and second annular matrix polymer regions and, optionally, coextruding therewith said fourth polymeric barrier layer and said third annular matrix polymer region.

67. (Withdrawn) The method of claim 62, wherein said first annular matrix polymer region and said first and second barrier layers comprise a material selected from the group consisting of ethylene vinyl acetate copolymers, copolymers of ethylene with acrylic acid or methacrylic acid, elastomeric polyurethanes and polyurethane copolymers, metallocene catalyzed polyethylene and polyethylene copolymers, ionomers, vinyl aromatic copolymers, silicones and mixtures thereof.

68. (Withdrawn) The method of claim 67, wherein said first annular matrix polymer region comprises an ethylene vinyl acetate copolymer having a vinyl acetate content of from about 19% to about 28% and said first and second polymeric barrier layers comprise a metallocene catalyzed polyethylene or polyethylene copolymer, or an ionomer.

69. (Withdrawn) The method of claim 68, wherein said first annular matrix polymer region comprises salicylic acid or a salt thereof as said microbial attachment/biofilm synthesis inhibitor, triclosan as said antimicrobial agent and bismuth subcarbonate as a radio-opacifying agent; and, said coextrusion is performed under conditions such that said salicylic acid or salt thereof does not preferentially partition to a surface of said first annular matrix polymer region or to a surface of said first or second polymeric barrier layers.

70. (Withdrawn) The medical device of claim 26, wherein at least one of said one or more barrier layers comprises a biodegradable polymer.

71. (Withdrawn) The medical device of claim 70, where said biodegradable polymer is selected from the group consisting of polylactic acid, polyglycolic acid and copolymers and mixtures thereof.

72. (Withdrawn) An implantable or insertable medical device comprising at least one biocompatible matrix polymer region comprising a material selected from the group consisting of ethylene vinyl acetate copolymers, copolymers of ethylene with acrylic acid or methacrylic acid, metallocene catalyzed polyethylenes and polyethylene copolymers, ionomers, vinyl aromatic copolymers, elastomeric polyurethanes and polyurethane copolymers, silicones and mixtures thereof; bioactive agents comprising an antimicrobial agent selected from the group consisting of triclosan, chlorhexidine and mixtures thereof; a microbial attachment/biofilm synthesis inhibitor selected from the group consisting of salicylic acid and salts and derivatives thereof; and, a radio-opacifying agent selected from the group consisting of bismuth subcarbonate, bismuth oxychloride, bismuth trioxide, barium sulfate, tungsten and mixtures thereof.

73. (Currently amended) A stent comprising

(A) a polymeric tubular shaft having more than one layer, said polymeric tubular shaft comprising a first annular layer comprising an extruded homogenous mixture of a matrix polymer, an antimicrobial agent and a microbial attachment/biofilm synthesis inhibitor;

(B) a first polymeric barrier layer at least partially covering an interior surface of said first annular layer; and

(C) a second polymer barrier layer at least partially covering an exterior surface of said first annular layer.

74. (Original) The stent of claim 73, wherein said stent is a ureteral stent.

75. (Previously Presented) The stent of claim 73, wherein said antimicrobial agent comprises triclosan and said polymeric tubular shaft comprises between 5 and 20 wt % triclosan.

76. (Original) The stent of claim 73, wherein said matrix polymer is an ethylenic copolymer.

77. (Original) The stent of claim 73, wherein said matrix polymer is an ethylene vinyl acetate copolymer.

78. (Original) The stent of claim 77, wherein said polymeric tubular shaft comprises between 60 and 80 wt % of said ethylene vinyl acetate copolymer.

79. (Original) The stent of claim 77, wherein said ethylene vinyl acetate copolymer has a vinyl acetate content between 19 wt % and about 28 wt %.

80. (Original) The stent of claim 73, wherein said stent further comprises a lubricious hydrophilic coating on an outside surface of said polymeric tubular shaft.

81. (Original) The stent of claim 73, wherein said polymeric tubular shaft comprises a plurality of apertures formed in the walls of the same.

82. (Original) The stent of claim 73, wherein said polymeric tubular shaft further comprises a radio-opacifying agent.

83. (Original) The stent of claim 82, wherein said radio-opacifying agent is bismuth subcarbonate.

84. (Original) The stent of claim 73, wherein said polymeric tubular shaft is a melt-extruded tubular shaft.

85. (Original) The stent of claim 73, wherein said polymeric tubular shaft has a wall thickness ranging from 0.2 mm to 0.8 mm.

86. (Original) The stent of claim 73, wherein said polymeric tubular shaft comprises end regions of different durometer value.

87. (Currently amended) A ureteral stent comprising

(A) a polymeric tubular shaft that is between 0.2 mm and 0.8 mm in wall thickness, said polymeric tubular shaft having more than one layer and comprising a first annular layer comprising an extruded homogenous mixture of a matrix polymer and a bioactive agent wherein:

(a) polymeric species of the matrix polymer ~~consisting~~ consists essentially of ethylene vinyl acetate copolymer ; and

(b) the bioactive agent ~~antimicrobial species consisting~~ consists essentially of triclosan;

(B) a first polymeric barrier layer at least partially covering an interior surface of said first annular layer; and

(C) a second polymer barrier layer at least partially covering an exterior surface of said first annular layer.

88. (Original) The ureteral stent of claim 87, further comprises a radio-opacifying agent.

89. (Original) The ureteral stent of claim 87, further comprising a lubricious hydrophilic coating on an outside surface of said polymeric tubular shaft.

90. (Original) The ureteral stent of claim 87, wherein said polymeric tubular shaft is a melt-extruded polymeric tubular shaft.

91. (Original) The ureteral stent of claim 87, wherein between 5 and 15% of the total triclosan in the stent is released after 30 days exposure to synthetic urine at a flow rate of 0.5 ml/min, and between 10 and 20% of the total triclosan in the stent is released after 90 days exposure to synthetic urine at a flow rate of 0.5 ml/min.

92. (Original) The ureteral stent of claim 87, wherein between 20 µg and 50 µg per day of triclosan is released after 90 days exposure to synthetic urine at a flow rate of 0.5 ml/min.

93. (Original) The ureteral stent of claim 87, wherein between 100 µg and 500 µg per day of triclosan is released after 30 days exposure to synthetic urine at a flow rate of 0.5 ml/min.

94. (Original) The ureteral stent of claim 87, wherein said polymeric tubular shaft comprises end regions of different durometer value.

95. (Previous Presented) The stent of claim 73, wherein the microbial attachment/biofilm synthesis inhibitor comprises a non-steroidal anti-inflammatory drug or a chelating agent.

96. (Previously Presented) The stent of claim 73, wherein the microbial attachment/biofilm synthesis inhibitor comprises a chelating agent selected from the group consisting of EDTA, EGTA and mixtures thereof.

97. (Previous Presented) The stent of claim 73, wherein the microbial attachment/biofilm synthesis inhibitor comprises a mixture of a non-steroidal anti-inflammatory drug and a chelating agent.

98. (Previously Presented) The stent of claim 95, wherein the non-steroidal anti-inflammatory drug comprises: salicylic acid or its derivatives or an acrylicarboxylic acid selected from the

group consisting of clidanac, ketorolac, ~~or~~ tinoridine and a salt or derivative thereof; and the chelating agent is selected from the group consisting of EDTA, EGTA and a mixture of EDTA and EGTA.

99. (Previously Presented) The stent of claim 97, wherein the non-steroidal anti-inflammatory drug comprises: salicylic acid or its derivatives or an acrylicarboxylic acid selected from the group consisting of clidanac, ketorolac, tinoridine and a salt or derivative thereof; and the chelating agent is selected from the group consisting of EDTA, EGTA and a mixture of EDTA and EGTA.

100. (Previous Presented) The stent of claim 73, wherein the stent further comprises a radio-opacifying agent comprising bismuth subcarbonate, and the stent further comprises a lubricious hydrophilic coating on an outside surface of said polymeric tubular shaft comprising a polyacrylic acid hydrophilic polymer.

101. (Previous Presented) The stent of claim 95, wherein the stent further comprises a radio-opacifying agent comprising bismuth subcarbonate, and the stent further comprises a lubricious hydrophilic coating on an outside surface of said polymeric tubular shaft comprising a polyacrylic acid hydrophilic polymer.

102. (Previous Presented) The stent of claim 73, wherein said matrix polymer comprises an ethylene vinyl acetate copolymer, the microbial attachment/biofilm synthesis inhibitor comprises a non-steroidal anti-inflammatory drug comprising ketorolac or a salt or derivative thereof, and the stent further comprises a radio-opacifying agent comprising bismuth subcarbonate, and the stent further comprises a lubricious hydrophilic coating on an outside surface of said polymeric tubular shaft

103. (Previous Presented) The stent of claim 73, wherein the antimicrobial species comprises triclosan or chlorhexidine.

U.S. Serial No. 10/789,398
Attorney Docket No. 98-P0151US2
Examiner Thomas Sweet

104. (Previous Presented) The stent of claim 102, wherein the antimicrobial species comprises triclosan or chlorhexidine.